REMARKS/ARGUMENTS

By the present Amendment, claims 1-5, 24, 25, and 42-44 are pending in this application. Claims 6-23, 26-41, and 45-59 were previously withdrawn as being directed towards non-elected subject matter. Applicants reserve the right to file one or more continuation, continuation-in-part or divisional applications towards any withdrawn subject matter. Claims 1, 4, and 24 have been amended. Basis for these amendments may be found throughout the specification and claims as originally filed, for example, in paragraph [0063] of U.S. 2007/0232661. No new matter has been added.

Claim Rejections - 35 U.S.C. §112

Claims 1-5, 24, 25, 42, 43 and 44 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement. Specifically, the Action alleges that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the claimed invention. Applicants respectfully traverse this basis for rejection.

The Action alleges that the instant application does not contain any working examples of the claimed compounds of Formula I; that no assays are described in which any of the compounds of Formula I were examined and their results obtained; and that no data of results have been disclosed with regard to any biological or chemical assays in terms of the efficacy of the claimed compounds on the claimed diseases or on inhibiting activation of signaling pathways such as the Hedgehog pathway.

Applicants respectfully submit that satisfying the enablement requirement of § 112, first paragraph does not turn on whether an example is disclosed in the application. See M.P.E.P. § 2164.02. The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of

experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988).

Applicants respectfully submit that the instant claims are directed to compounds of Structure (I), (II), and claim 24 that inhibit a hedgehog signaling pathway. Applicants further submit that the specification as originally filed provides ample guidance to make the presently claimed compounds without undue experimentation. For example, paragraphs [0256] to [0261] of the specification discloses that the presently claimed compounds can be readily prepared using known synthetic methodology, including using combinatorial chemistry for generating libraries of these compounds (see, U.S. 2007/0232661).

Applicants further submit that the skilled artisan would appreciate that the specification as originally filed provides ample guidance to test the claimed compounds of Structures (I), (II), and claim 24 as inhibitors of a hedgehog signaling pathway using experimentation typical in the art of small molecule screening assays. For example, the specification discloses that libraries of compounds were screened as hedgehog modulators using techniques described in Chen *et al.*, PNAS 99:14071-14076 (2002); see paragraph [0264] of US 2007/0232661). Clearly, one having ordinary skill in the art would not encounter any undue experimentation in employing the assays disclosed in Chen *et al.* to determine the ability of the presently claimed compounds of Structure (I), (II), and claim 24 to inhibit a hedgehog signaling pathway. Accordingly, Applicants respectfully submit that one having ordinary skill in the art could make and/or use the presently claimed compounds without undue experimentation.

The Action further alleges that the physiological activity of the presently claimed compounds would be unpredictable because the various claimed moieties are not art-recognized equivalents. Applicants respectfully disagree and provide herewith, experimental evidence that a representative number of the presently claimed compounds of Structure (I), (II) and claim 24

comprising each class of the various claimed R groups possess the claimed activity of inhibiting a hedgehog signaling pathway.

Applicants submit herewith, a Declaration by Dr. Philip A. Beachy ("the Declaration") that provides experimental data showing that compounds of Structure (I), (II) and claim 24 comprising each class of the various claimed R groups share the common claimed activity of inhibiting a hedgehog signaling pathway. Applicants note that compounds of Structure (I) are representative of the genus of compounds claimed in claim 24.

Using the assay described in Chen *et al.*, 2002, which is referenced in the as-filed specification, Dr. Beachy and those working under his direction determined the inhibitory concentration at which compounds 1-7 of Structure (I) and 8-9 of Structure (II) inhibit 50% of the activity of a Sonic hedgehog induced Gli responsive firefly luciferase reporter.

Dr. Beachy used Shh-LIGHT2 cells, which contain a TK promoter-Renilla luciferase control for normalization and a Sonic hedgehog induced Gli responsive firefly luciferase reporter to measure the effects of compounds on a hedgehog signaling pathway.

Shh-LIGHT2 cells were treated with an active N-terminally truncated form of Sonic hedgehog (ShhNp) (4 nM) and compounds 1-9 (see claims 3 and 5) for two days and then the luciferase activities were measured from the cell lysates by luminometry using a dual luciferase assay (Promega). Compounds were tested in varying concentrations to determine the concentration of each compound required to achieve 50% inhibition of Sonic hedgehog induced Gli responsive firefly luciferase reporter activity (IC_{50}).

Table 1 in the Declaration summarizes the IC_{50} values for compounds 1-9 measured in the Shh-LIGHT2 assay. The results show that compounds of Structures (I), (II), and claim 24 have a common physiological activity of inhibiting a Hedgehog signaling pathway. Compounds 1-7 of Structure (I) have alkyl R_1 groups such as ethyl, propyl, and pentyl, and R_2 and R_3 groups such as hydrogen, alkyl, halogen, alkoxyl, acetyl and nitro groups. Compounds 8-9 of Structure (II) have R_5 groups such as chlorine and *tert*-butyl, and R_6 groups such as bromine and nitro

groups. Thus, compounds of Structures (I), (II), and claim 24 comprising each class of the claimed R groups are represented in the data.

Applicants submit that the Declaration shows that each class of the presently claimed R groups comprises a common physiological activity of inhibiting a Hedgehog signaling pathway. Assuming *arguendo*, that the various claimed R groups themselves are not art-recognized equivalents, in the context of the presently claimed compounds as a whole, these various claimed R groups contribute to a common physiological activity of inhibiting a Hedgehog signaling pathway. Thus, the exemplified compounds are representative of the genus of presently claimed compounds of Structure (I), (II), and claim 24, because the various claimed R groups possess the claimed activity of inhibiting a hedgehog signaling pathway. Moreover, Applicants point out that screening libraries of compounds in assays such as the Shh-LIGHT2 assay is considered typical in the art of small molecule screening.

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

Accordingly, Applicants submit that the specification as originally filed fully enables the instant claims and that one having ordinary skill in the art would be able to practice the entire breadth of the claims without undue experimentation. Reconsideration and withdrawal of this basis for rejection is respectfully requested.

Claim Rejections - 35 U.S.C. §103

Claims 24, 42, 43, and 44 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Hcaplus 1999:48617 (Reference U: WO 99/01127 and/or U.S. Patent No. 6,515,027) in view of Patani *et al.* (Reference V: Chem. Rev. 1996, 3147-3176). It is alleged that it would have been obvious to one of ordinary skill in the art to modify the prior art compounds to structurally similar compounds that are bioisosteres of one another. Applicants respectfully traverse this basis for rejection and submit that the Action fails to establish a *prima facie* case of obviousness against the presently claimed invention.

Applicants respectfully submit that the Action has failed to establish a *prima facie* case of obviousness with respect to the presently claimed subject matter (*See, In re Mayne,* 104 F.3d 1339 (Fed. Cir. 1997); the USPTO has the burden of showing a *prima facie* case of obviousness). The Examiner must at a minimum demonstrate that the combined references teach or suggest all the claim features (*See, In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974)), and even assuming, *arguendo*, that the combination of references teaches each claim feature, the Examiner must provide an explicit, apparent reason to combine these features in the fashion claimed by the Applicant with a reasonable expectation of success. *See, KSR v. Teleflex, Inc.*, No. 04-1350 at 4, 14 (U.S. Apr. 30, 2007) ("A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art").

In the instant case, the Action has not provided sufficient rationale to support why the prior art would have led the skilled artisan to modify the prior art compounds identified by the Examiner and arrive at the presently claimed inhibitors of a hedgehog signaling pathway with any reasonable expectation of success.

The Action alleges that the difference between the prior art compounds and the instantly claimed compounds is the teaching of a phenyl ring in the prior art as a replacement of the pyridyl ring in the instant compounds. The Action further alleges that one having skill in the art would be motivated to modify the phenyl group (ethylated) of the compounds of Hcaplus

1999:48617 with pyridyl groups (ethylated) as presently claimed, because Patani *et al.* allegedly teach that phenyl and pyridyl rings are bioisosteric replacements of one another that result in retention of biological activity within different series of pharmacological agents. Applicants respectfully disagree.

Applicants submit that Hcaplus 1999:48617 does not teach or suggest any compound that inhibits a hedgehog signaling pathway. In contrast, Hcaplus 1999:48617 teaches substituted benzanilides that act as ligands, agonists or antagonists of the CC chemokine receptor CC-CKR5.

Applicants further submit that Patani *et al.* state:

> "A lead compound with a desired pharmacological activity may have associated with it undesirable side effects, characteristics that limit its bioavailability, or structural features which adversely influence its metabolism and excretion from the body. Bioisosterism represents one approach used by the medicinal chemist for the rational modification of lead compounds into safer and more clinically effective agents."

Accordingly, one having ordinary skill in the art at the time of invention would not have been motivated or had any reason to select the compounds of Hcaplus 1999:48617 to modify as suggested by the Examiner because Hcaplus 1999:48617 does not disclose that the compounds identified therein have the claimed activity of inhibiting a hedgehog signaling pathway. In addition, there is no art of record that suggests that the compounds disclosed in Hcaplus 1999:48617 have such activity. Applicants submit that the one having ordinary skill in the art at the time of invention would not have any reasonable expectation of successfully arriving at the instantly claimed compounds, by choosing a lead compound from Hcaplus 1999:48617 because none of the compounds taught therein were known to have the desired pharmacological activity. If the prior art does not teach any specific or significant utility for the disclosed compounds, then the prior art is unlikely to render structurally similar claims prima facie obvious in the absence of any reason for one of ordinary skill in the art to make the reference compounds or any structurally related compounds. *In re Stemniski*, 444 F.2d 581, 170 USPQ 343 (CCPA 1971). See M.P.E.P. § 2144.09 (VI).

Moreover, there would be no motivation or reason to improve an unknown property of a compound without employing impermissible hindsight. The *KSR* court noted that "[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. See, *Graham*, 383 U. S., at 36 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to 'guard against slipping into the use of hindsight'" (quoting *Monroe Auto Equip-ment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F. 2d 406, 412 (CA6 1964))). See also, e.g., *Ecolochem, Inc. v. Southern California Edison Company*, 227 F.3d 1361, 1371 (Fed. Cir. 2000) (("[One] 'cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.'") (quoting *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988)).

Accordingly, Applicants submit that Patani *et al.* does not cure the insufficiencies of Hcaplus 1999:48617; thus, these references collectively fail to establish a *prima facie* case of obviousness against the instant claims.

Applicants respectfully submit that Patani *et al.* teaches that bioisosteres elicit similar biological activity due to common physiochemical properties (see p. 3148, second paragraph). Patani *et al.* disclose, for example, that fluorine, hydroxyl groups, and amino groups are biosteric replacements for hydrogen (see p. 3152); that chlorine, bromine, thiol, and hydroxyl groups are suitable monovalent substitutions for each other (see pp. 3154-3155); that oxygen, sulfur, amine, and selenium can serve as divalent replacements involving double bonds (see p. 3155); and that benzene rings, thiophene rings, and pyridine rings are biosteric replacements. Applicants submit that there is no guidance offered in Hcaplus 1999:48617, Patani *et al.*, nor in any of the art of record that teaches or suggests, which of the various bioisosteric replacements is preferred over another and which atom of a lead compound should be modified by bioisosteric replacement in order to achieve a desired activity with any reasonable expectation of success.

Applicants further submit that the Federal Circuit has established that in order to find a *prima facie* case of unpatentability in modification of a prior art compound to yield a claimed

compound, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required. *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492. F.3d 1350 (Fed. Cir. 2007) (citing *In re Jones,* 958 F.2d 347 (Fed. Cir. 1992); *Dillon*, 919 F.2d 688; *Grabiak*, 769 F.2d 729; *In re Lalu*, 747 F.2d 703 (Fed. Cir. 1984)). The *Takeda* Court concluded that such a test for *prima facie* obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*.

Applicants respectfully submit that the Action has clearly failed to provide a sufficient basis or rationale that would lead one having ordinary skill in the art at the time of invention to modify the prior art compounds as suggested by the Examiner in order to arrive at the instantly claimed compounds with any reasonable expectation of success. Thus, the Action has failed to establish a *prima facie* case of obviousness against the presently claimed compounds.

For all these reasons, Applicants respectfully request reconsideration and withdrawal of these rejections.

CONCLUSION

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved, the Examiner is requested to contact the undersigned at the telephone number given below so that a prompt disposition of this application can be achieved.

A petition for a one month extension of time under 37 C.F.R. §1.136(a) accompanies this response. The Commissioner is hereby authorized to charge $65.00 as the fee for the one month extension of time to Deposit Account No. 07-1896, referencing the above-identified Attorney Docket Number.

A Request for Continued Examination (RCE) under 37 CFR §1.114 accompanies this response. The Commissioner is hereby authorized to charge $405.00 as the fee for the RCE to Deposit Account No. 07-1896, referencing the above-identified Attorney Docket Number.

No additional fees are believed to be due with the present communication, however, the Commissioner is hereby authorized to charge any other fees that may be due in connection with the filing of this paper, or credit any overpayment to Deposit Account No. 07-1896, referencing the above-identified Attorney Docket Number.

Respectfully submitted,

Date: May 3, 2010

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